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# Mesogenic sugars. From aldoses to liquid crystals and surfactants



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Amphiphilic sugar derivatives, formed by condensation of functionalized aliphatic chains with aldoses, form liquid crystals, in most cases smectic. A puzzling observation was the failure of the *S,S*-acetals of 6-deoxy sugars, *L*-rhamnose and *D*-fucose, to form such phases. A satisfactory model to explain this behavior involves—in most cases—the formation of columns, which are destabilized with the deoxy sugars in which the apolar end methyl groups are pushed together.

Despite the abundance of chiral centers in the mono- and disaccharides used the smectic phases themselves in general display no chirality. By appropriate molecular design in which the amphiphilic character was deliberately suppressed it was possible to prepare glucose derivatives that

exhibit chiral nematic phases as well as impressive helical twisting powers. Simple condensation chemistry is used to produce such derivatives.

The amphiphilic character can be deliberately enhanced, and this is readily achieved in double headed 'gemini' derivatives formed by condensation of glucose or lactose with a long chain diamine followed by reduction followed by acylation of the nitrogen atoms with long chain acyl anhydrides. The thermodynamics of micellization of precursors to these derivatives have been studied. The gemini derivatives themselves display remarkable properties including the formation of giant vesicles and an appreciable capacity for the solubilization of hydrocarbons.

After receiving his MSc in organic chemistry from the University of Groningen in 1985, Henk van Doren accepted a position at the Netherlands Institute for Carbohydrate Research (NIKO-TNO, which has recently become part of TNO Nutrition and Food Research Institute) in Groningen. His research on the synthesis and properties of carbohydrate-derived liquid crystals allowed him to obtain his PhD with Professor R. M. Kellogg in 1989. After spending six months as a visiting Assistant Professor at the Department of Crystallography in Pittsburgh, he returned to NIKO-TNO to work on carbohydrate-derived liquid crystals and surfactants and on the chemical modification of polysaccharides. In 1997 he moved to the TNO facility in Zeist, The Netherlands, where he has become Product Manager, Nonfood Applications in the Department of Carbohydrate Technology. Henk is the (co-) author of about 30 publications and several patents.

Dr Elly Smits was born in Groningen in 1969. She studied chemistry at the University of Groningen and graduated in 1993 in physical organic chemistry. She did her PhD research at the

NIKO-TNO Institute for Carbohydrate Research in Groningen in cooperation with the University of Groningen, on carbohydrate-derived liquid crystals under the guidance of Professor R. M. Kellogg and Professor J. B. F. N. Engberts. Currently she has a post-doctoral position at the Department of Microbiology of the University of Groningen where she is working on the bacterial lactose transporting membrane protein LacS.

Dr J. Monique Pestman was born in 1970. She majored in physical organic chemistry at the University of Groningen. After graduating cum laude in 1994, she started her PhD research on carbohydrate surfactants at the NIKO-TNO Institute for Carbohydrate Research in Groningen in cooperation with the University of Groningen and under the guidance of Professor J. B. F. N. Engberts and Professor R. M. Kellogg. Monique defended her thesis entitled 'Carbohydrate-Derived Surfactants Containing an *N*-Acylated Amine Functionality' in November 1998. In December of the same year, she started working as a sales and marketing manager for TNO Nutrition and Food Research Institute.



Elly Smits



Henk A. van Doren



Monique Pestman



Jan B. F. N. Engberts



Richard M. Kellogg

Professor Jan B. F. N. Engberts (born 1939) obtained his PhD degree in physical organic chemistry in Groningen in 1967. After a postdoctoral position in Amsterdam with Professor Th. J. de Boer, he returned to Groningen where he currently has the chair in Physical Organic Chemistry. His research is largely focused on organic chemistry in water: reactivity, catalysis, surfactant chemistry and membrane mimetic chemistry. His work has been published in 380 papers and three patents. His hobbies include horseback riding and process philosophy.

Professor Richard M. Kellogg (born 1939) obtained his PhD degree at the University of Kansas in 1965. He has carried out research in various areas including free radical kinetics, photochemistry, macrocyclic chemistry and various aspects of catalysis. He has a chair of Organic Chemistry at the University of Groningen and has held administrative positions including dean of the chemistry department. He is currently director of the Stratingh Institute of Chemistry and Chemical Technology. He has about 250 publications and several patents.

## 1 Introduction

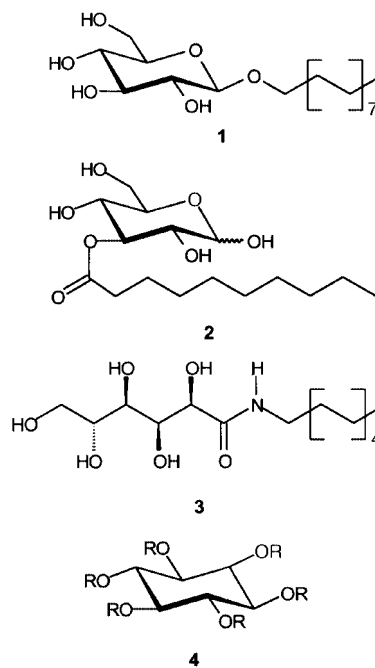
Although the words are neutral it takes little to imagine the frustration on the part of these superb experimentalists when Emil Fischer and Burckhart Helferich wrote in 1911 (from the German): 'The cetyl glycoside is tasteless. It does not have a sharp melting point. Near 78 °C it starts to soften. At approximately 110 °C it melts to transparent droplets that flow together to form a colorless fluid with a clear meniscus near 145 °C. We have not been able to find the reason for this irregularity of the melting point'. The foregoing is a description of the melting point behaviour of *n*-hexadecyl  $\beta$ -glucopyranoside (**1**), a compound that Fischer and Helferich *knew* to be in all respects pure. Probably this is the earliest report of a synthetically obtained liquid crystal derived from a carbohydrate.<sup>1</sup>

More than a quarter of a century later Noller and Rockwell<sup>2</sup> recognized the phenomenon for what it was, namely that between 78 and 145 °C compound **1** exists in a liquid crystalline form. *Mesogenic* behaviour in sugar derivatives was first recognized as a common occurrence by G. A. Jeffrey.<sup>3</sup> 'Mesogenic' is the term commonly used to describe, respectively, the compound itself and the intermediate 'meso' phase, such as is formed with **1**. It is now clear that many simple sugar derivatives (oligo- and polysaccharides do not fall within the present discussion) can have mesogenic phases. The most straightforward way to achieve this is to ensure that the compounds are *amphiphilic*, that is to say with a *hydrophilic* sugar head group and a *hydrophobic* tail. The compounds **1–4** shown in Scheme 1 are examples of such amphiphiles and all behave as mesogens.

The types of liquid crystalline phase (mesophase) formed can differ greatly. For example, compounds **1–3** form layered smectic A phases (the characteristics of the various phases will be discussed later) whereas **4**, developed by Praefcke *et al.*,<sup>4</sup> forms columnar discotic phases in keeping with the disk-like molecular structure. Although liquid crystals have been studied intensely for many years and find extensive use in commercial applications, sugar mesogens have only lately come into the mainstream of attention.

## 2 Mesogenic sugars

We became interested in these types of mesogens in 1985. Huge amounts of starch and sugar are produced in the area surrounding Groningen. There was interest on the part of the

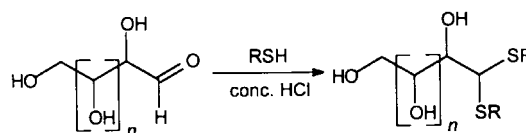


Scheme 1

Netherlands Institute for Carbohydrate Research (NIKO, now TNO Nutrition and Food Research Institute) in developing high value added sugar derivatives. The observations described briefly above stimulated us to begin fundamental work on developing unusual sugar derivatives, using small molecules, in general mono- and sometimes disaccharides. We entered this area as chemists interested in molecular design and not as specialists in liquid crystals. We have discovered that the two worlds can work together productively but that it is necessary first to learn the language in order to be able to communicate with the natives. A travelogue has been composed from the standpoint of chemists visiting the land of mesogens. This review, thematically based on our own work, is written, in accordance with the goals of *Chemical Society Reviews*, also for the interested novice.

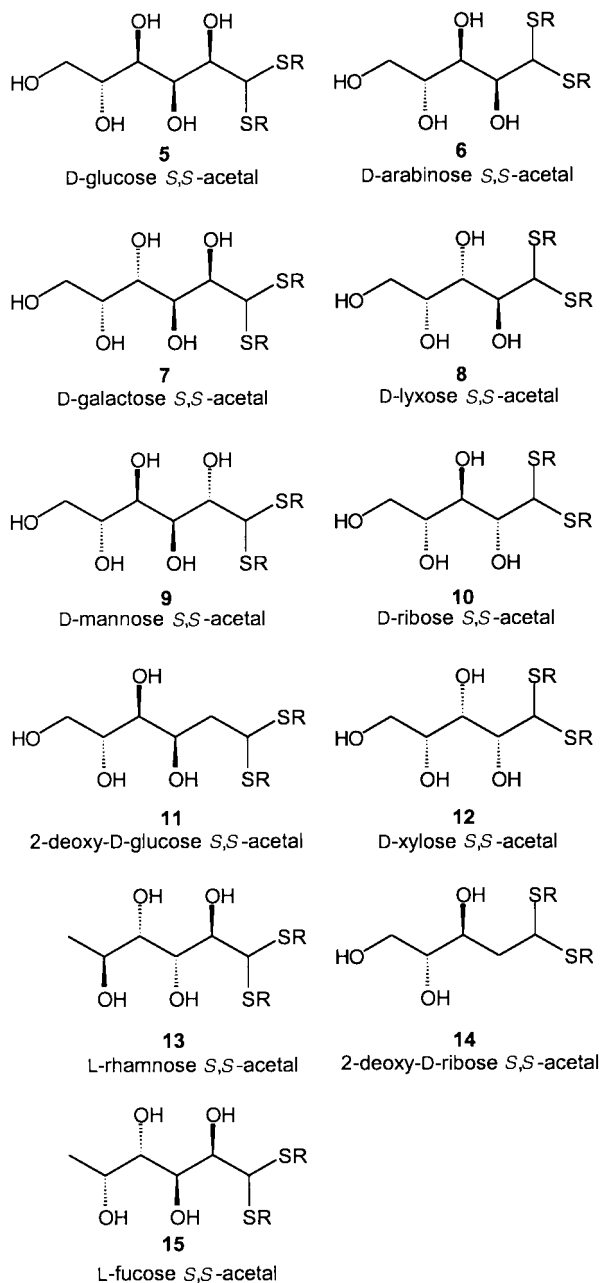
We began with thiol rather than alcohol or amine derivatives of the sugars in the hope that thiol condensation products would be less susceptible to bacterial degradation. Even today it is still not clear whether this hope has any foundation in fact. The effects of stereochemistry of the sugar and the effect of alkyl chain length on liquid crystalline behaviour were first examined. These investigations led us on to other areas including surfactants. We will describe here systematic insights gained through the years and will try to do this in broadly understood terms, guiding the reader through the jargon-ridden jungle of liquid crystallinity and related matters.

Preparation of dithioacetals of aldoses is usually simple (Scheme 2).



Scheme 2

The aldose is dissolved in a small volume of concentrated HCl and two equivalents of alkanethiol are added; small amounts of thioglycoside are formed but these are readily removed (this cyclization is, of course, the reaction that one wants to avoid). The richness of stereochemical variation obtainable on use of simple monosaccharides is illustrated with compounds **5–15** (Scheme 3).



Scheme 3

At chain lengths of R of 6–8 carbon atoms, dependent on the sugar, liquid crystallinity was systematically observed.<sup>5</sup> What exactly does one see? Take, for example, the D-glucose derivative **5** with R = *n*-octyl. The crystals, when observed under a (polarizing) microscope, undergo a melting transition at 98.3–100.3 °C and transform to a sticky ‘mesophase’, in which birefringence is observed up to a temperature of 116.6 °C, at which point the birefringence disappears and a clear melt (‘isotropic solution’) forms. As measured by differential scanning calorimetry (DSC) the first transition involves an enthalpy  $\Delta H$  of 47.0 kJ mol<sup>−1</sup> and the second a  $\Delta H$  of 1.3 kJ mol<sup>−1</sup>. On cooling the mesophase is formed again and eventually crystallization occurs. The temperatures for the mesophase to solid phase transition during cooling are different from those for the solid phase to mesophase transition during heating (*hysteresis*). This type of mesogenic behaviour on heating and cooling is termed *enantiotropic* (not to be confused with stereochemical nomenclature) as opposed to *monotropic* whereby on heating molecules undergo a transition directly from the crystalline to the isotropic phase but on cooling form a liquid crystalline phase before crystallization occurs.

Although the onset temperatures for **5**–**15** vary slightly as a function of the length of the chains R as well as the individual sugars—after all the stereochemistries are not identical—there is little in the way of systematic relationships. One less than obvious trend is this: ideally the acyclic sugar derivatives will adopt linear all-*trans* conformations. Should the stereochemistry be such that a 1,3-*syn* interaction between hydroxy groups develops, buckling of the chain takes place and a bent or sickle-shaped conformation can become more stable. These 1,3-*syn* interactions lead to mild depressions of the melting point.

By far the most remarkable observation, however, is that *none* of the dithioacetal derivatives of the 6-deoxy sugars L-rhamnose **13** and L-fucose **15** show liquid crystalline behaviour. In Fig. 1 the behaviour of the series of D-glucose *S,S*-acetals compared to L-rhamnose *S,S*-acetals is shown.

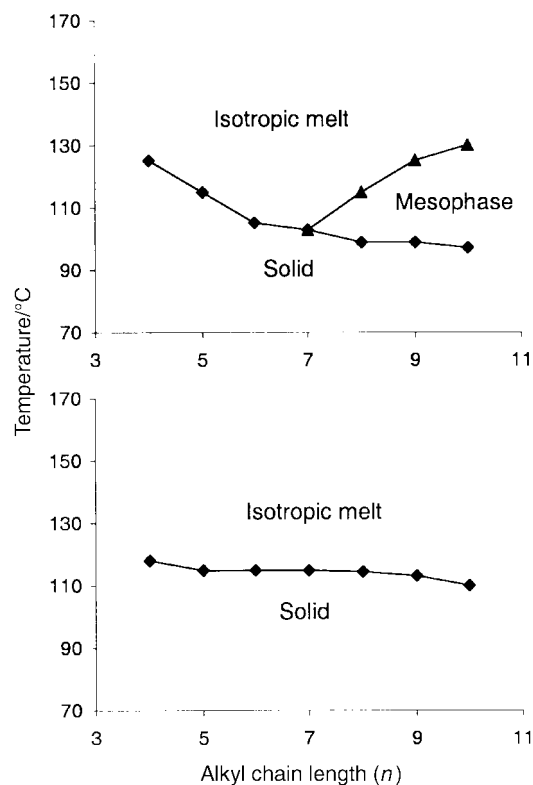


Fig. 1 The transition temperatures of a series of D-glucose *S,S*-acetals (above) and L-rhamnose *S,S*-acetals (below) plotted as a function of the number of carbon atoms in the alkyl chains (◆ melting point, ▲ clearing point).

Why this large difference in behaviour? A detour will be necessary to prepare the answer. There are three broad categories of *thermotropic* liquid crystals that can be formed (‘thermotropic’ means that only thermal changes are required to induce mesogenic behaviour in the pure compounds). Each category has a wide, often intimidating, array of subdivisions. We were reasonably confident that we were dealing with *smectic* phases. Such phases are usually highly viscous (‘syrupey’), a point that can be confirmed with the unaided eye. In a *smectic* phase the individual molecules are arranged parallel to each other to form layers and in the case of amphiphilic sugar derivatives the layers are arranged so that the sugar molecules (head groups) can contact each other (head-to-head) to form intermolecular hydrogen bonds. This is two dimensional ordering. A rough analogy (of a single layer) is a closely packed marching band; to effect a change of direction closely coordinated action and a high degree of cooperativity (‘viscous’ behaviour) is required. Subcategories of *smectic* arrangements are in essence the consequence of various tilting arrangements and/or additional ordering within the layers.

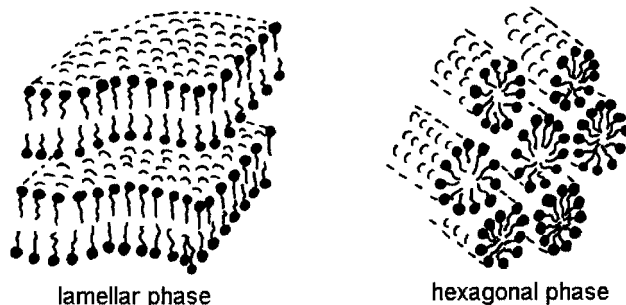
The phases were not *nematic*. Nematic phases are usually more fluid and lack the syrupey, sticky characteristics of *smectic*

phases. Nematic phases have only one-dimensional ordering in which the individual molecules are oriented parallel along their long axes (such long, thin molecules are often termed *calamitic*). A large school of fish provides a reasonable analogy; they all go in the same direction and as a group make cooperative movements although each fish has considerable freedom of movement independent of neighbouring fish. In nematic liquid crystals dipole–dipole interactions and mutual polarisability are forces that hold the arrangement together. On a macroscopic scale a swirling can occur whereby macroscopic helicity (that is to say helical structures consisting of many, non-covalently bonded molecules) is formed. If the twist is biased either towards right- or left-handedness then a *cholesteric* phase exists (cholesterol benzoate is a prime example of this). The currently more popular term *chiral nematic* is for practical purposes synonymous with cholesteric and will be used here as such.

In *discotic* liquid crystals the molecules are arranged in columns. Sometimes, but not always, this occurs with molecules that are themselves disk-shaped. A group of sky-jumpers holding hands so that they form a circle is a reasonable analogy for a single such molecule. Various phases are illustrated in Scheme 4.

Although not immediately necessary for the current discussion this is a good point at which to introduce also some basic nomenclature for *lyotropic* phases. Lyotropic phases are formed when amphiphiles such as the sugar derivatives discussed here interact with a solvent, usually water. The commonest lyotropic liquid crystalline phase is the *lamellar* or  $L_\alpha$  phase (Scheme 5), which is formed by a stack of ordered bilayered aggregates separated by aqueous layers. The head groups are in contact with water and the (sometimes interdigitated) alkyl chains are located on the inside of the bilayer. Variations in temperature and structure can induce changes in packing.<sup>6</sup> The resemblance to the thermotropic smectic phase is obvious. The *hexagonal* phase consists of long cylindrically shaped micelles, which are packed into a hexagonal array with a diameter 1.5–2 times the molecular length, and are surrounded by an aqueous phase. At low water content amphiphiles with a large hydrophobic section can form an inverted hexagonal phase in which the head groups are arranged around cylinders of water, and the alkyl chains fill the space between the hexagonally ordered water-containing inner compartments. The analogy with thermotropic discotic phases is clear. Finer subtleties of all these phases are discussed in the literature.<sup>7</sup>

Identification of phases is not a task for amateurs. Phases can be studied by DSC and by thermal microscopy in which melting behaviour is examined with the aid of a polarizing microscope. Textures of thermotropic liquid crystalline phases can be observed and photographed and compared with handbooks of known phases.<sup>8</sup> Photographs of phases, particularly in color, can be spectacular and of artistic merit; one of us (HvD) has obtained through the years an impressive collection. Powder X-ray diffraction (Guinier) can give valuable information about spacing. Again reference to known phases can be made and



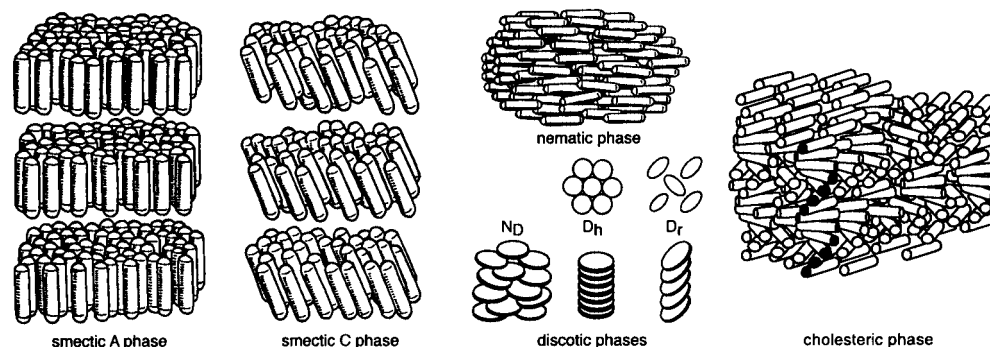
Scheme 5

experience is invaluable. Finally, miscibility studies are highly informative. If a known liquid crystalline phase is miscible with an unknown phase (the experiments require experience and a good eye), the two phases are identical (smectic, nematic, etc.).<sup>9</sup>

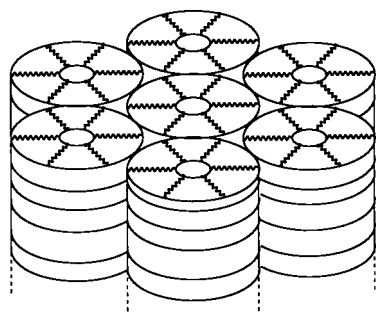
## 2.1 Encounter with the unexpected

To return to compounds **5–15**: we made an error on our first venture into this area (the previous paragraph is thus written from bitter experience). Based on a comparison with known textures and the fact that all nondisk-like carbohydrate mesogens reported at that time displayed smectic A phases, we had no reason to conclude that the dithioacetals behaved in a different fashion. This left us with no explanation for the lack of liquid crystallinity in L-rhamnose and D-fucose derivatives **13** and **15**. However, closer inspection of Guinier X-ray photographs revealed low intensity lines at first unseen, and led, after reinterpretation, to the conclusion that the molecules are packed in discotic phases in nearly the same fashion as in the lyotropic inverted hexagonal phase ( $H_{II}$ -phase).<sup>5c</sup> This means that *columns* are formed in which the head groups form the cores. The hydrophobic tails extend out in a rather disorganized fashion so that a disk-like arrangement is formed. From the observed spacings (the average distance between columns) it appears that the tails of different disks are locked into each other like the interlocked fingers of two hands (interdigitated) as illustrated in Scheme 6. This immediately provides a plausible explanation of why the L-rhamnose and D-fucose derivatives have no liquid crystalline phase—the apolar methyl groups at the desoxy end cannot readily be pushed together.

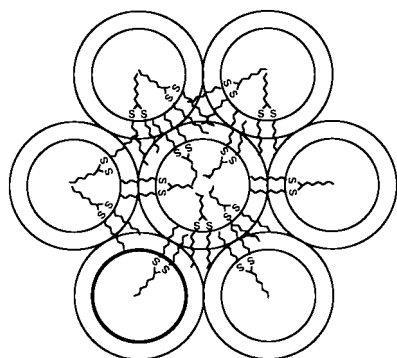
As more and more amphiphilic carbohydrate derivatives were reported, with ever more variation in the size and number of alkyl chains, it became clear that their mesogenic behavior can be predicted on the basis of the relative sizes of the hydrophilic and hydrophobic parts present in the molecule. Derivatives with only one alkyl chain (nearly) always form smectic A phases, analogous to the lyotropic lamellar phases, whereas most derivatives with two alkyl chains will form columnar hexagonal phases (compare to the inverted hexagonal— $H_{II}$ —phase). We



Scheme 4



Proposed structure of hexagonal columnar mesophase



Possible arrangement of molecules of the di-(*n*-octyl) *S,S*-acetal of **7** in the mesophase

Scheme 6

have also been able to show that increasing the size of hydrophilic head groups may eventually again lead to columnar hexagonal phases, in this case similar to the 'normal' hexagonal—H<sub>I</sub>—phases.<sup>7c</sup> In Section 6, Table 2 the regularities between the size and nature of the individual molecules and aggregational behaviour are discussed further.

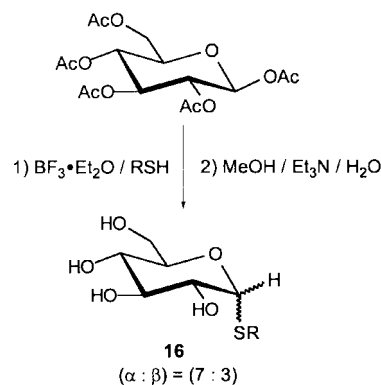
### 3 Chirality

This is a good point at which to note a recurring phenomenon. Despite the abundance of chiral centers in each molecule, the liquid crystalline phases obtained displayed no chirality. Such a statement causes organic chemists with a solid background in molecular chirality to inquire whether they have heard correctly. The molecules themselves are of course chiral and nonracemic. 'No chirality' refers to the fact that the *phases*—as supramolecular aggregates—display no phase selective interactions with polarized light. In chiral nematic (cholesteric) phases the chiral director, *i.e.* the vector that defines the length direction of the molecule, is propagated from molecule to molecule in a helical sense. In essence the wavelength of phase sensitive refracted polarized light is a measure of the distance between the grooves of the helix; the shorter the wavelength, the tighter the helix. Chiral smectic phases (smectic C in Scheme 4) are known; the directors must be propagated helically in some fashion from layer to layer, a process which requires a considerable degree of cooperativity. If a *chiral nonracemic molecule*, an amphiphilic sugar derivative, for example, is arranged perpendicularly to the plane of the layer, the phase itself is *achiral*. A rough analogy to the above arguments is this: imagine that one were to mold an (achiral) sphere from wet starch, each polymer chain of which is richly provided with chiral centers. The eye perceives only the bulk sphere, which as an object is achiral. On the other hand if one molds a screw from the same wet starch this is chiral. In other words, the chirality of

the bulk morphology is probed, not that of the individual components.

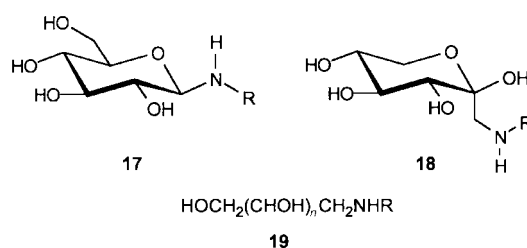
### 4 Synthetic methods and targets

Before proceeding further with mesogenic sugars something should be said about their synthesis. Although the chemistry of mono- and disaccharides is enormously rich in possibilities, the choices are limited by the requirement of relatively cheap, high yield processes that do not require excruciating purification protocols and which allow the synthesis of homologous series of compounds from common precursors. Our preference is to start from D-glucose, if possible, owing to its availability (the reader should realize that we are going to deal only with monosaccharides and that we will not enter into the chemistry of polysaccharides). Industrial scale syntheses of alkyl glycosides are carried out by direct condensation of D-glucose and alcohols but the purity is not high. If one wants pure materials it is often better in our experience to start from β-D-glucose pentaacetate. By way of illustration thioglucoopyranosides **16** of D-glucose with alkanethiols are prepared readily as shown in Scheme 7. Deacylation, required if one starts from glucose pentaacetate, is readily accomplished in virtually quantitative yield with trimethylamine-methanol.<sup>10a</sup>



Scheme 7

An even simpler reaction is the condensation of *monoalkyl amines* with *unprotected* D-glucose in ethanol to form 1-amino-D-glucopyranosides **17**, the β-anomers of which can be crystallized selectively (Scheme 8). However, in solution anomerization occurs rapidly. It is obvious that the challenge in these types of reactions is control of the α/β selectivities, which usually entails finding a balance between thermodynamic and kinetic control.

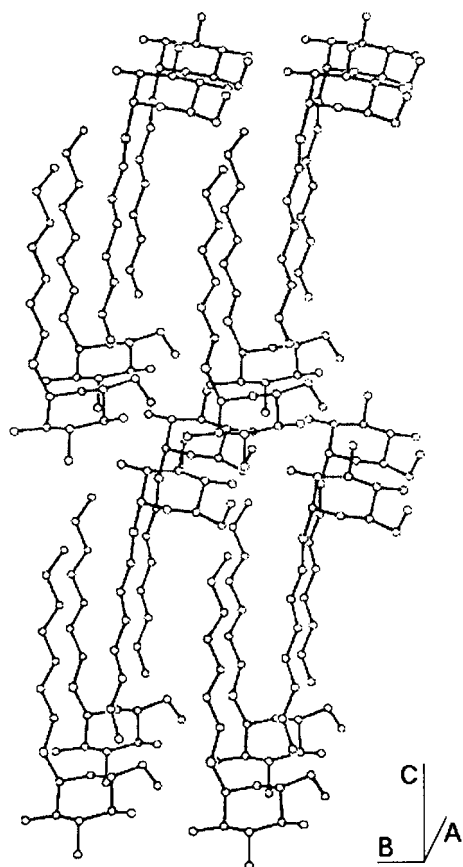


Scheme 8

The Amadori rearrangement provides a good entry to 1-amino-1-deoxy-β-D-fructopyranosides **18**, whereas linear 1-amino substituted derivatives **19** are obtained by condensation of the non-protected sugar with an amine under reductive conditions. These compounds are also illustrated in Scheme 8.

These reactions, supplemented with methods for selective protection, have formed a practical basis for synthetic efforts.

Let us take a practical example of the preparation and study of a series. After some modification of literature procedures, a series of *n*-alkyl 1-thio- $\alpha$ -D-glucopyranosides **16** was prepared. Modification was necessary to exploit the observation that in this case the  $\beta$ -anomer is the kinetic product, which rearranges under acid catalyzed conditions to the thermodynamically more stable  $\alpha$ -anomer. Deprotection is readily achieved. The behaviour of the  $\alpha$ -*n*-heptyl derivative of **16** is typical. Between 97 and 138 °C a liquid crystalline phase is formed that was unambiguously identified as smectic A<sub>d</sub> (see reference 8 for a discussion of the characteristics of the textures of the A<sub>d</sub> and other phases). A crystal structure (Fig. 2) of the compound gives



**Fig. 2** Molecular packing in the crystal of heptyl 1-thio- $\alpha$ -D-glucopyranoside (**16**, R = C<sub>7</sub>H<sub>15</sub>).

considerable insight into how the liquid crystalline phase must be assembled (we assume that important characteristics of the crystal phase are maintained in the liquid crystal with the proviso that major crystal-to-crystal transitions do not occur prior to melting).<sup>10b</sup> The molecular packing involves 'up-down' arrangement of individual molecules with a high degree of interpenetration (interdigitation) of alkyl chains. These 'up-down' arrangements form a layer that interconnects to the next layer by hydrogen bonding of the sugar head groups. In other words a typical *nonchiral* smectic double layer is formed except that the head groups (sugars) do not point in the same direction but alternate. Quite similar packing had already been observed by Jeffrey<sup>3</sup> for *n*-octyl  $\alpha$ -D-glucopyranoside. This compound has long been known to have a liquid crystalline phase.

The experiences described above led to formulation of two different projects that, to our minds at least, addressed fundamental questions. The first was how to express the chirality of the sugars on a supramolecular scale. In terms of molecular design this problem reduces to the discovery of compounds that do not stack into layers leading to smectic

phases, but which will generate *nematic* liquid crystalline phases. This entails *designed suppression* of the amphiphilic character.

In the second project molecular design was used to exploit, rather than suppress, the amphiphilic character of the sugar derivatives. This has led, among other things, to the design of an unusual class of amphiphiles, which show promise for applications.

## 5 Supramolecular chirality

First the problem of supramolecular chirality. The failure to express supramolecular chirality in the sugar derivatives mentioned above stems from the fact that the sugars are too sugary. The amphiphilic character is reinforced by the many hydroxy groups that readily enter into hydrogen bonding. This leads to rigidly packed double layers that assemble to smectic phases. How does one design an alternative, and, before doing so, what are the structural requirements of such an alternative? Chirality, supramolecular chirality to be more precise, is in general more readily expressed in nematic phases (one-dimensional ordering). Molecules that form nematic phases should be long and rod-like ('*calamitic*' and '*anisotropic*' are terms encountered in this context; the former refers to the shape and the latter to the fact that the properties within the molecule are dependent on direction). Many are multi-component, as illustrated schematically in Scheme 9, in which some common building blocks are shown.

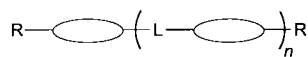
The tendency of the hydroxy groups in sugars to enhance amphiphilic character had already been recognized by others. Weiss *et al.*<sup>11a</sup> have penta-acylated D-glucose with *trans*-3,4-dialkoxycinnamic acids and have obtained materials that form *achiral* discotic mesophases whereas Watanabe *et al.* have prepared glucose derivatives that exhibit chiral discotic nematic phases.<sup>11b</sup> The hydroxy groups of sugar derivatives can also be removed by chemical manipulation: compounds **20** and **21** prepared, respectively, by Vill *et al.*<sup>12</sup> and Wong *et al.* (Scheme 10),<sup>13</sup> do form chiral mesophases, but at the cost of quite drastic chemical manipulations.

We centered our design around D-glucose and resolved only to use condensation chemistry, which proceeds readily in good yield and which allows structural variation. In order a) to use the sugar as the core and b) to ensure rigidity in the sugar derivatives as well as two points of attachment for c) a group that promotes mesogenic behaviour as well as an appropriate tail, D-glucose is locked in a *trans*-decalin structure **22** whereby R<sup>2</sup> is attached *via* normal condensation chemistry to the anomeric carbon and R<sup>1</sup> by condensation of an aldehyde across the 4,6-position. That such chemistry proceeds cleanly is well known from literature precedent. Mesogenic groups can be placed either in sections R<sup>1</sup> or R<sup>2</sup>. In this approach the 2,3-hydroxy groups are left unchanged.

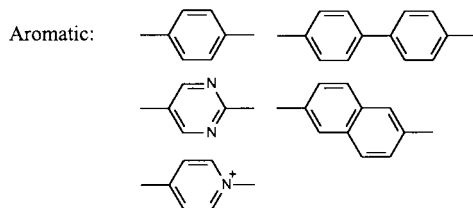
The molecular design starts with condensation of the anomeric carbon either with an alkanethiol **23** (glucose pentaacetate with RSH-BF<sub>3</sub> for 15 min to allow isolation of the kinetically controlled  $\beta$ -product followed by deacylation with Me<sub>3</sub>N-H<sub>2</sub>O) or with 4-alkoxyphenols **24** under analogous conditions. The choice of a 4-substituted phenol was based on observations of Baeyens-Volant<sup>14</sup> and Tschierske<sup>15</sup> that incorporation of a rigid spacer unit provided with an alkyl chain stabilizes mesophases. Fortunately the reaction of glucose pentaacetate with phenols provides exclusively the  $\beta$ -products (Scheme 11).<sup>16</sup> As mentioned previously the acetate protecting groups can readily be removed.

As one anticipates these condensation products have liquid crystalline phases starting at a four carbon chain for **23** and a six carbon chain for **24**. The melting and clearing temperatures as a function of length of the alkyl chains are plotted in Fig. 3.

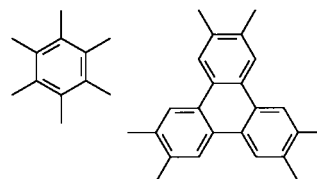
Schematic structure of a calamitic liquid crystal



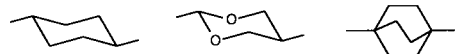
Core groups:



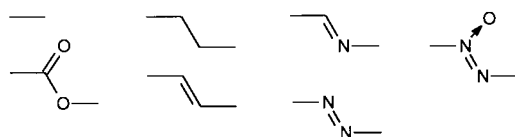
For discotic liquid crystals:



Alicyclic and Heterocyclic:



Linking groups: L

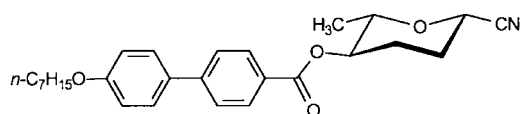


Terminal groups: R

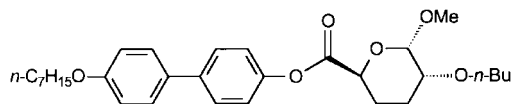
alkyl, alkoxy

polar groups: CN, NCS, F, Cl, CF<sub>3</sub>

Scheme 9



20

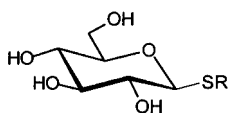


21



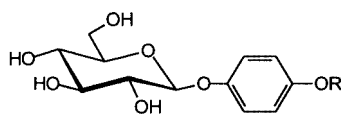
22

Scheme 10



23

R = *n*-C<sub>5</sub>H<sub>11</sub>, *n*-C<sub>10</sub>H<sub>21</sub>, *n*-C<sub>12</sub>H<sub>25</sub>



24

R = CH<sub>3</sub>, *n*-C<sub>10</sub>H<sub>21</sub>, *n*-C<sub>12</sub>H<sub>25</sub>

Scheme 11

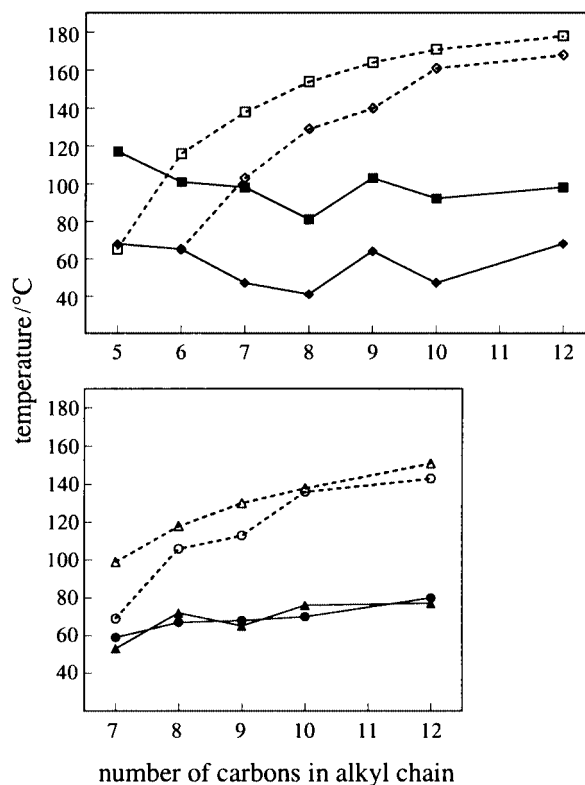


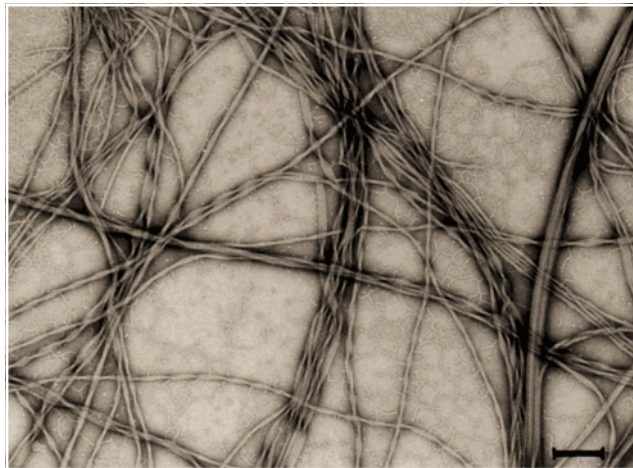
Fig. 3 Melting and clearing temperatures of  $\alpha$ -23 (■, □) and  $\beta$ -23 (◆, ◇) (above) and  $\alpha$ -24 (▲, △) and  $\beta$ -24 (●, ○) (below).

Data for the  $\alpha$ -anomers are taken from the literature.<sup>10c</sup> The behaviour is characteristic for such series; the temperature range between melting and clearing (liquid crystalline state) increases with chain length and then reaches an apparent maximum. The alkyl 1-thio- $\alpha$ -D-glucopyranosides clearly have a smaller range of liquid crystallinity than the  $\beta$ -anomers. As anticipated from



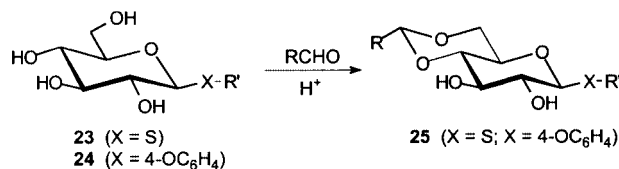
the literature the 4-alkoxyphenyl derivatives have in general slightly higher clearing points indicative of stabilization of the liquid crystalline state.

The thermotropic liquid crystalline states were identified as smectic  $S_A$ , which as a phase is achiral. Lyotropic liquid crystals are also formed on contact with water. The structures of the latter can be spectacular. In Fig. 4 an electron micrograph of **24** ( $R = \text{nonyl}$ ) is shown. These types of derivatives often show such very long, intertwined strands.



**Fig. 4** Ribbons formed by compound **24** (electron micrograph, negative staining, the bar represents 200 nm).

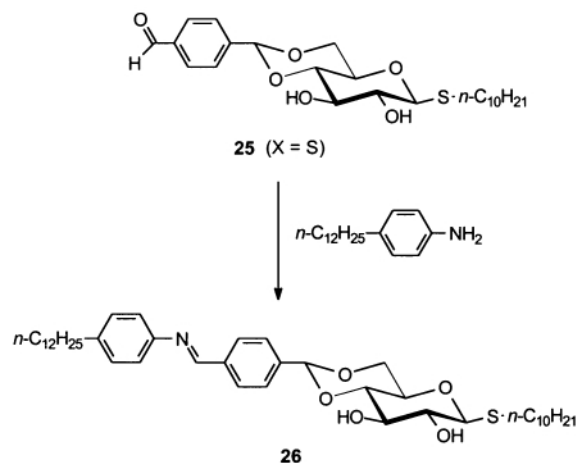
The next step on the road to the final goal, the (*R*)-4,6-*O*-acetals, which embody the *trans*-decalin skeleton, is condensation with an aldehyde, which will bear the mesogenic group. The aldehyde substituent will end up in the preferred equatorial position, consistent with the indicated *R* absolute configuration. Various aldehydes can be condensed across the 4,6-positions of **23** and **24** using methanesulfonic acid or pyridinium tosylate as the acid catalyst (Scheme 12).



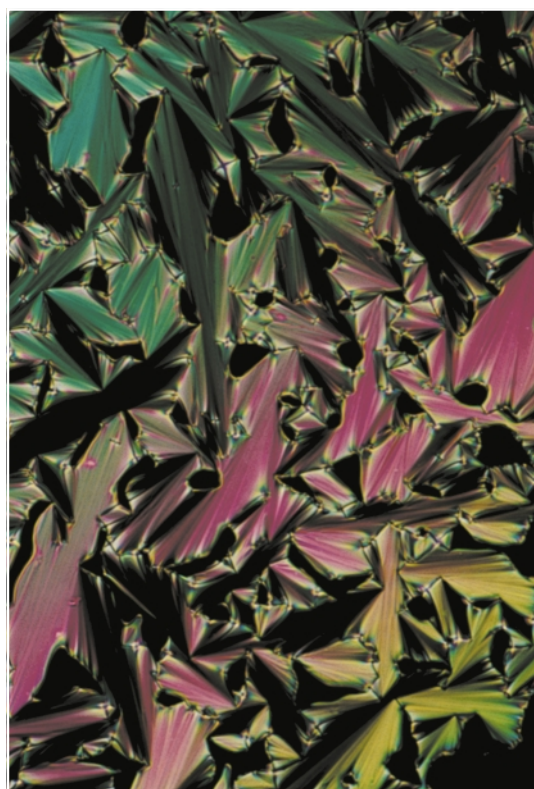
**Scheme 12**

Aliphatic and aromatic aldehydes, even with electron withdrawing ( $4\text{-NO}_2$ ,  $4\text{-CHO}$ ) or electron donating ( $4\text{-OCH}_3$ ,  $4\text{-CH}_3$ ) substituents can be condensed provided care is taken to adjust the conditions for differences in reactivity. The thermodynamically more stable equatorially substituted derivatives were always observed. A strategy of 4,6-protection of  $\text{D-glucose}$ , followed by acetylation at the 1-, 2- and 3-positions, and condensation at the anomeric carbon and concluded with deprotection can also be followed although in general this route is more laborious and involves the danger of (partial) loss of the 4,6-*O*-acetal.

Much hope was vested in Schiff base **26** (Scheme 13), which seemed to have the proper characteristics at the anomeric carbon (a 4-alkoxyphenol can, of course, also be used, and these compounds have been prepared and show similar behaviour). The 4-carbaldehyde substituent on the phenyl ring of **25** allows construction of mesogens. For example, condensation with 4-*n*-dodecylaniline delivers the desired **26**. Schiff base derivatives are known to be extremely potent mesogens. Indeed a liquid crystalline phase is formed between 127 and 158 °C. The view in a polarizing microscope is spectacular. The texture obtained on cooling from the isotropic melt is shown in Fig. 5.



**Scheme 13**

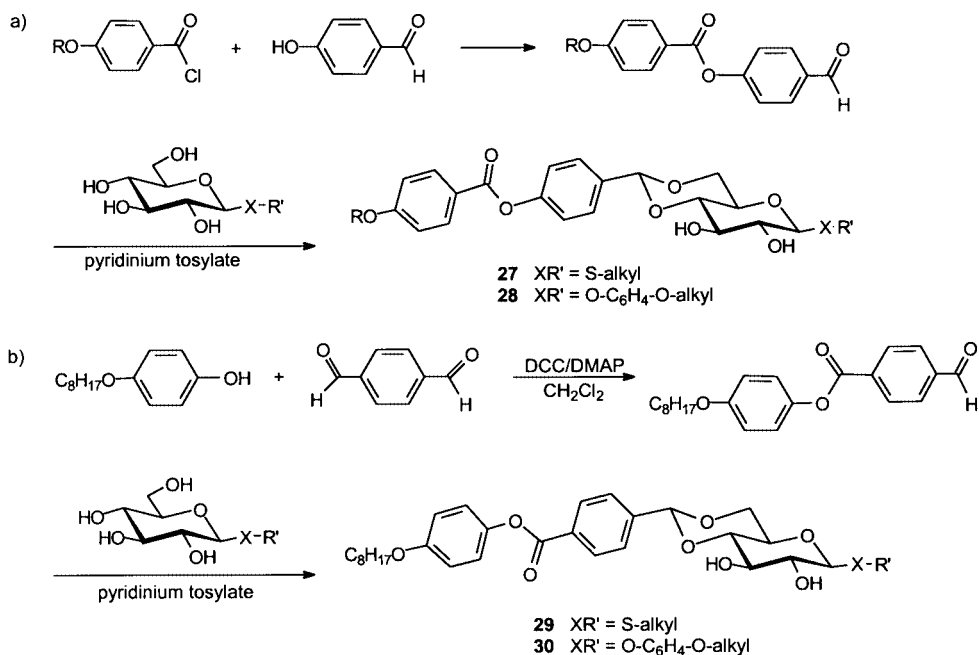


**Fig. 5** Focal-conic fan-like texture of the  $S_A$  phase of **26**. Magnification 200 $\times$ .

From the texture we conclude that a smectic A phase (achiral) has been formed. However, this phase is *not* miscible with the smectic A mesophase of amphiphilic liquid crystals like derivatives **23**, indicative of the fact that **26** at the very least organizes into a different (most likely monolayer) arrangement in the thermotropic liquid crystal.

The observation that the dominant nature of the hydroxy groups could be muted was encouraging although the desired obtainment of a cholesteric phase was not yet realized. Nevertheless, the general structural concept, as represented in **22**, seemed tenable. Effects are subtle, however. The seemingly minor operation (Scheme 14a,b) of changing the direction in which the ester group runs,  $\text{-C(O)O-}$  compared to  $\text{-OC(O)-}$ , has a drastic effect on phase behaviour as described below. Of course, the overall dipole of the mesogenic unit is strongly affected by this 'minor' change.<sup>17</sup>

First, however, another consideration. As already seen the block  $R^1$  (structure **22**) can be designed to contain a mesogenic group and  $R^2$  a hydrophobic chain. This sequence may be

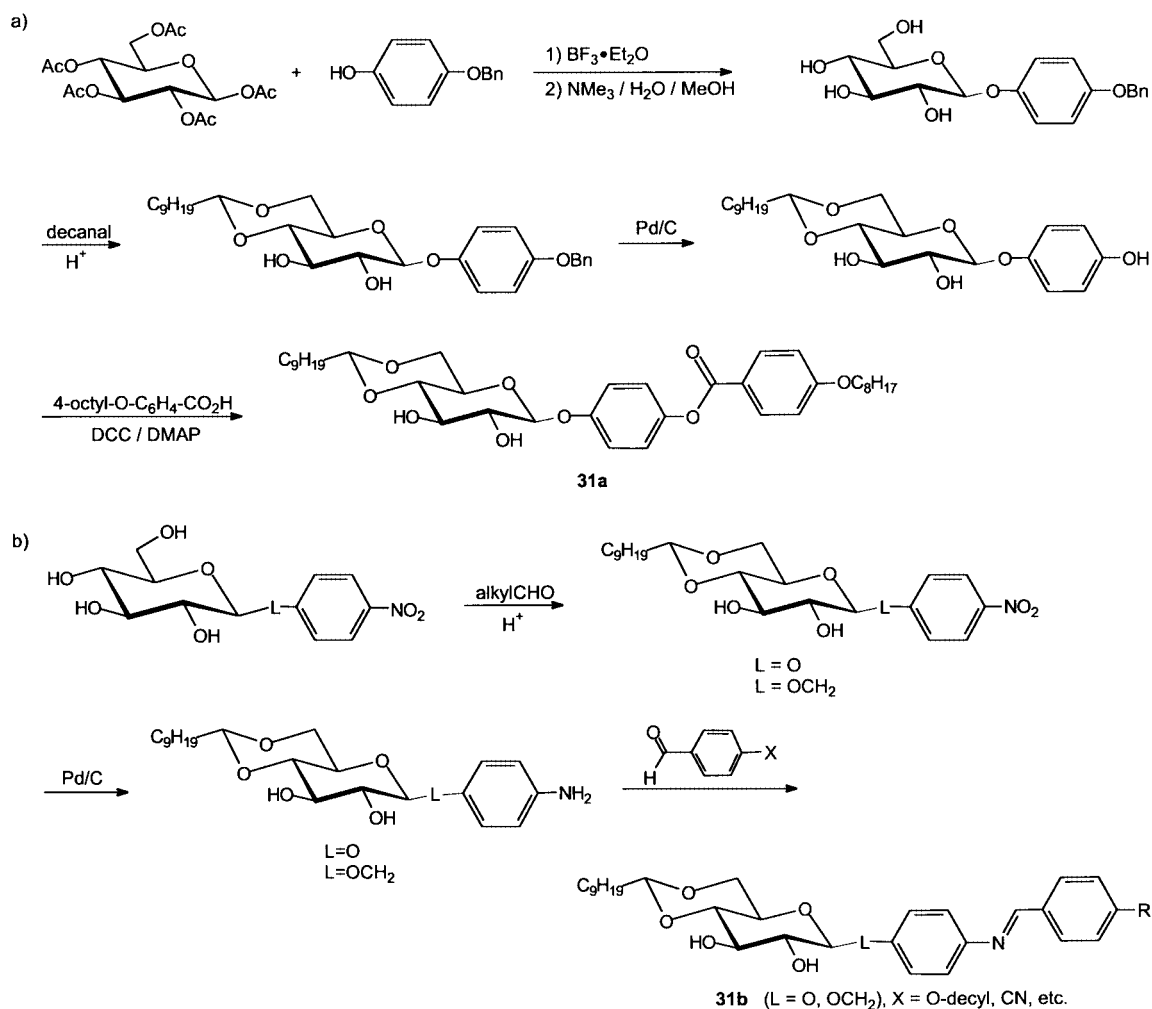


Scheme 14

reversed. For example, in **31a,b** the mesogenic unit is attached *via* the anomeric carbon atom (Scheme 15a,b).

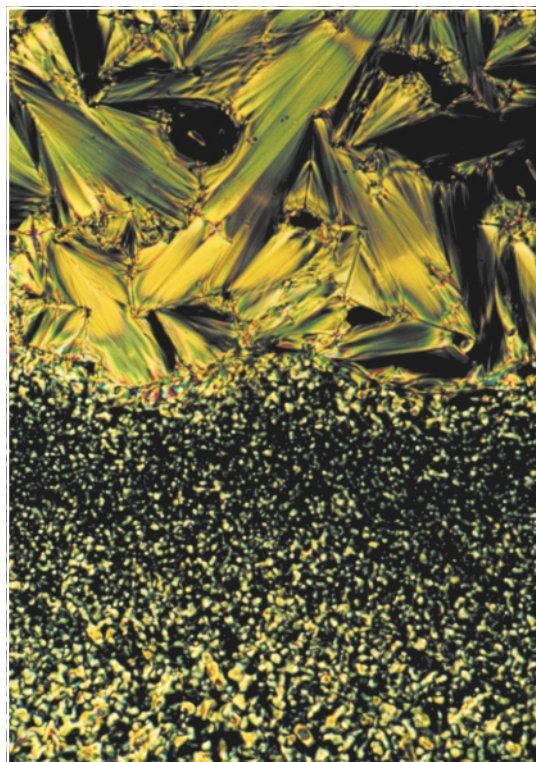
As an illustration of the sensitivity of liquid crystalline behaviour to seemingly minor structural changes, in **31b** if  $\text{L} = \text{O}$  no liquid crystallinity is observed whereas if  $\text{L} = \text{OCH}_2$  (two atoms instead of one) liquid crystallinity (smectic, unfortu-

nately) is observed. The difference likely lies in the fact that with a one atom linker a bend is enforced on the molecule at the cost of the required calamitic character of the molecule. With a two atom linker a more linear molecular geometry can be attained and as a consequence the molecules are liquid crystalline.



Scheme 15

To our great satisfaction compounds **27** and **28** with  $\text{XR}' = \text{S-alkyl}$  or  $-\text{OC}_6\text{H}_4\text{O-alkyl}$  exhibit chiral nematic phases. But **29** and **30**, which have the ester unit running in the opposite direction, form smectic phases! By extensive fine tuning finally in **27** (and **28**) the proper combination to give the desired chiral nematic phases has been found. How do we know? In Fig. 6 the



**Fig. 6** The  $\text{S}_\text{A}$  phase of the Schiff base derivative **26** is not miscible with the cholesteric phase of the ester derivative **27**. Magnification 200 $\times$ .

results of a miscibility study are shown. The texture change running horizontally through the middle of the photograph marks the delineation between two immiscible phases, namely the cholesteric phase of **27** (lower half) with a known smectic phase of Schiff base **26**. This suggests that the new phase is non-smectic; the assignment of a chiral nematic phase is based on comparison of the texture with known samples. The grainy focal-conic fan-like texture observed is also characteristic of chiral nematic phases.

What does one do with chiral nematic phases and why did we want to prepare such phases outside of the scientific challenge of demonstrating that macroscopic chirality in sugar derivatives can be attained? The obvious application of low molecular weight compounds that form nematic phases is to use them in small amounts as dopants to induce chirality in nematic host materials.<sup>18</sup> There is great interest in 'sergeant-soldier' effects whereby a chiral dopant, not even necessarily optically pure, propagates chirality to achiral bulk surroundings, for example, an achiral commercial nematic phase.

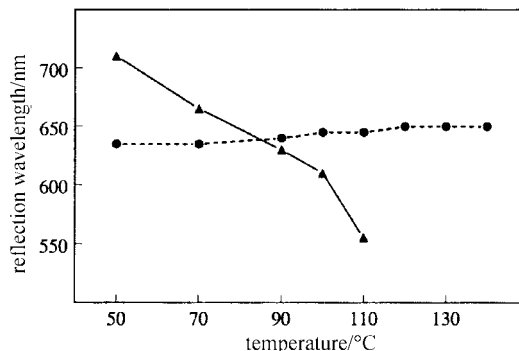
The *pitch*  $p$  is indicative of the degree of helicity. Circularly polarized light of the same handedness as the helical aggregate is reflected at wavelengths that depend on the pitch. The relationship is

$$p = n \cdot \lambda_{\text{max}}$$

where  $n$  is the refractive index and  $\lambda_{\text{max}}$  the reflection wavelength. Mixture of a cholesteric phase with a short pitch (the small molecule dopant) with a nematic phase, as long as the phases are *compatible* (mutually soluble), leads to induction of chirality in the bulk; the dilution effect widens the pitch to correspond to the wavelengths of visible light and thus makes it observable. Extrapolation of plots of effective pitch against

concentration to 100% concentration allows one to estimate the natural pitch.

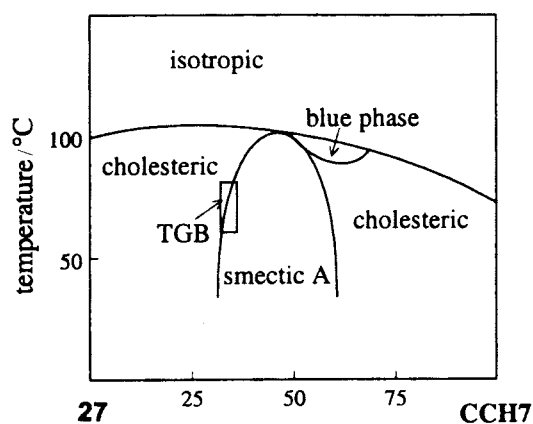
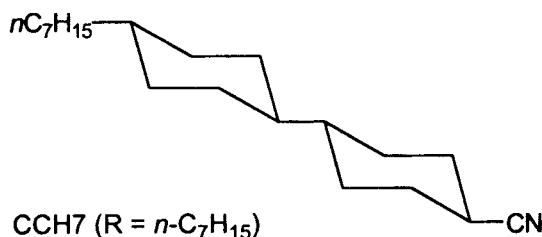
Compound **26** was added to a diacrylate known commercially as 'C6M' (Fig. 7), which is a readily available and polymerizable nematic used, for example, in filters for polarised light.<sup>19</sup> A mixture containing 9.65% w/w of **26** in C6M exhibits a cholesteric phase between 50 and 113  $^\circ\text{C}$  and shows selective reflection. The pitch decreases with increasing temperature as shown in Fig. 7.



**Fig. 7** Temperature dependence of the cholesteric helix of a mixture of **26** in C6M, before ( $\blacktriangle$ ) and after ( $\bullet$ ) polymerisation.

After polymerization (70  $^\circ\text{C}$ , irradiation with 1% w/w initiator) the pitch is observed to be shortened owing to shrinkage during polymerization but is now, as anticipated, independent of temperature.

The complexity of liquid crystalline behaviour is nicely illustrated by an experiment wherein **27** is dissolved in 'CCH7', which is also a commercial liquid crystalline nematogen. The qualitative phase diagram for different ratios of **27** and CCH7 is shown in Fig. 8.



**Fig. 8** Qualitative phase diagram of a mixture of **27** and CCH7.

Clearly a chiral nematic phase is present over a broad concentration range. However, at intermediate ratios a smectic A phase is also observed as well as a 'blue' phase (probably blue phases are highly ordered chiral mesophases with a double helix structure) and a TGB phase ('Twist Grain Boundary', which

consists of blocks with a  $S_A$  structure separated by sections of uncertain structure).

The propensity to induce a helical twist, known as the helical twisting power (HTP), defined as  $1/\beta_M$ , where

$$\beta_M = (PXr)$$

$P$  = pitch,  $X$  = mole fraction of chiral dopant and  $r$  = enantiomeric ratio (1 in our case) of these additives, is remarkably high. The HTP's are derived by extrapolation of dilution experiments and are given in Table 1.

**Table 1** Helical twisting powers (HTP) of selected compounds

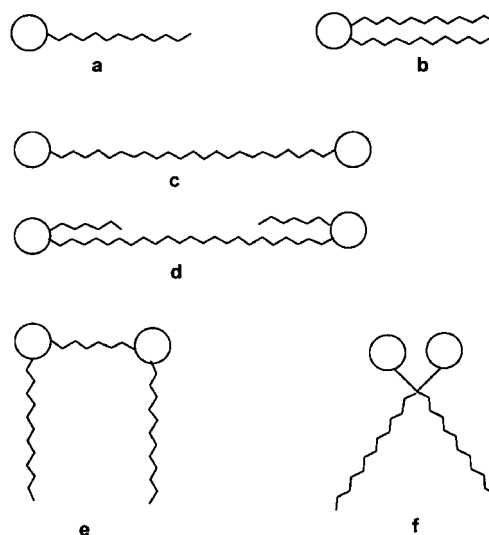
Compound	HTP/ $\mu\text{m}^{-1}$
28-8O,O6	55
28-8O,O12	57
27-8O,10	23
27-8O, $\alpha$ 8	64

By way of comparison cholesteryl laurate has an HTP of  $12 \mu\text{m}^{-1}$  and cholesteryl cetyloxybenzoate  $10 \mu\text{m}^{-1}$ .<sup>20</sup> The carbohydrate derivative 2,5-di(*p*-hexyloxybenzoyl)-dianhydro-D-glucitol has an HTP of  $62 \mu\text{m}^{-1}$ .<sup>20</sup> HTP values of up to  $115 \mu\text{m}^{-1}$  have been reported for mono- and bis-aminoanthraquinone derivatives but these compounds are poorly compatible.<sup>21</sup> It is clear that these sugar derivatives have both high HTP values and good compatibility, characteristics that make these compounds attractive for applications.

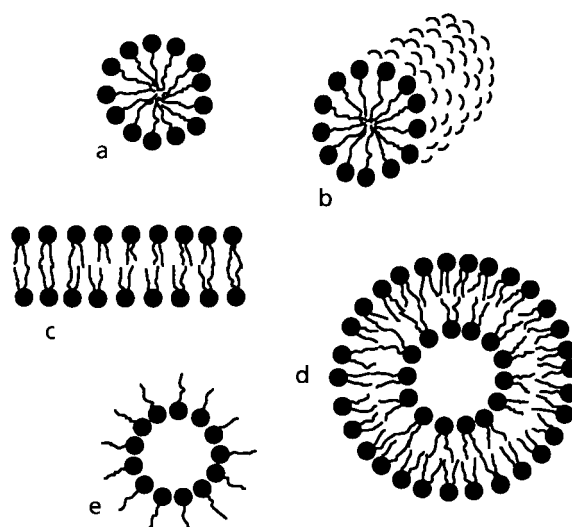
## 6 Unusual amphiphiles

In the foregoing section the emphasis lies on preservation of liquid crystallinity while muting amphiphilicity in order to force the formation of chiral nematic phases. At the other extreme one could deliberately enhance amphiphilic character in order to profit from the surfactant properties associated with that character. The link with liquid crystalline behaviour is obvious: if put in water the amphiphilic molecules that so readily aggregate into thermotropic phases express the same tendencies in the form of micelle formation. The amphiphilic character can be influenced almost at will by varying the number and type of head groups.

In contrast to the slow development of interest in liquid crystals derived from mono-(or di-)saccharides, cheap and biodegradable amphiphilic sugar derivatives with surface-active properties have long been, and remain, the object of serious interest, both industrial and academic. Some aspects of amphiphilic molecules with surfactant properties are given as an aid to discussion. Such compounds may have ionic (sulfate, phosphate, carboxylate, trialkylammonium) or nonionic (polyalcohols in general) head groups. The former are probably better known and have received more attention. Conventional surfactants consist of a head group and one or more alkyl chains (a or b in Fig. 9).<sup>22</sup> There is, however, growing interest in more daring structural variation in amphiphiles. Molecules that have a hydrophilic head group at both ends of a hydrophobic chain are referred to as *bolaamphiphiles*<sup>23</sup> represented by c and d. *Gemini* surfactants, a term introduced by Menger,<sup>24</sup> contain, in the definition of Menger, in sequence a long hydrocarbon tail, an ionic group, a rigid spacer, a second ionic group and another hydrocarbon tail. Currently, all surfactants with two hydrophilic groups and two hydrophobic tails and a mirror plane or  $C_2$  axis are referred to as *gemini* surfactants, even if no spacer is present<sup>25</sup> as represented by e and f. *Gemini* surfactants, almost all of which reported so far have ionic head groups, have unusual properties, including the not surprising capacity—in



**Fig. 9** A single-chained surfactant (a); a double-chained surfactant (b); bolaamphiphiles (c and d) and gemini surfactants (e and f).



**Fig. 10** Various aggregate morphologies: a micelle (a), cylindrical micelle (b), bilayer (c), vesicle (d) and inverted micelle (e).

view of the bifunctionality—to associate into polymer-like aggregates (thread-like micelles and similar phenomena).<sup>26</sup>

The commonest types of aggregates formed from amphiphiles are illustrated in Fig. 10. These drawings, although only schematic, of micelles (a), cylindrical micelles (b), bilayers (c), vesicles (d) and inverted micelles (e) give a reasonable idea of potential aggregates. Fortunately, there are quite systematic relationships between structure and the type of aggregate formed. The type of aggregate formed by a surfactant in aqueous medium is often well predicted by the packing parameter  $P$ <sup>27</sup>

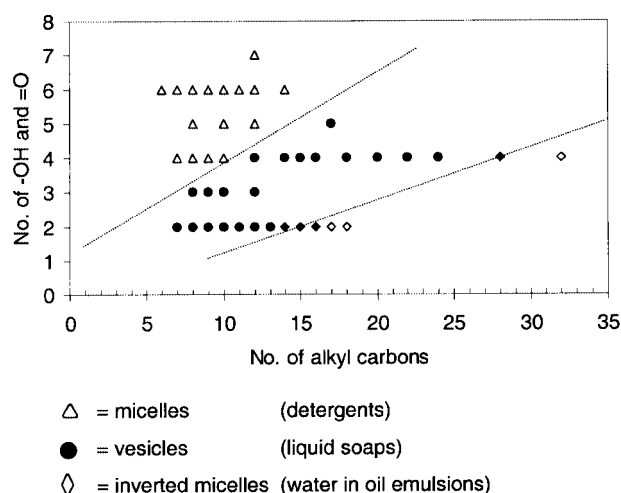
$$P = v/(a_o l_c)^{-1}$$

where  $v$  is the volume of the hydrophobic tail,  $l_c$  is the critical chain length, usually slightly less than that of a fully extended, all-*trans* chain) and  $a_o$  is the optimal cross-sectional surface area of the head group. In Table 2 the general relationships between surface geometry and preferred structure are summarized.

The data in Table 2 apply in principle to classical, *i.e.* single headed, ionic surfactants. It is, however, reassuring to see that for nonionic amphiphiles (surfactants) developed by us,<sup>28</sup> *e.g.* compounds **16**, **23**, **24**, **39** and **41**, there is an orderly transition from micelles to vesicles as a function of the number of hydroxy groups in the head group and the length of the hydrophobic tail (Fig. 11).

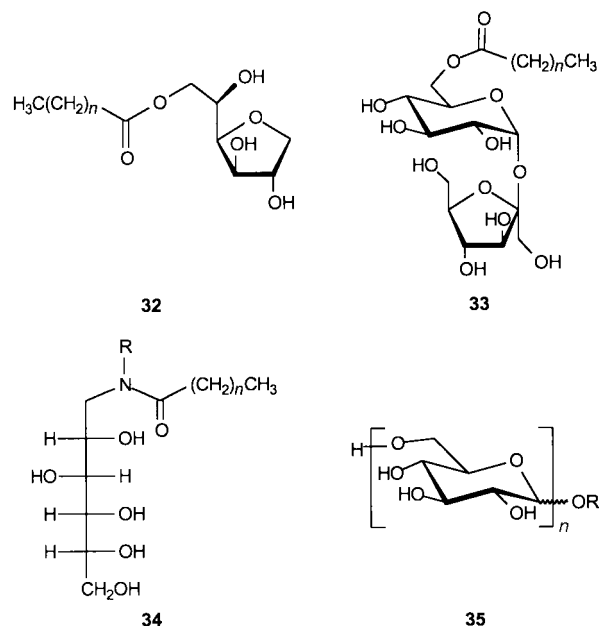
**Table 2** The relationship between surfactant shape and preferred structure

Packing parameter $v(a_0l_c)^{-1}$	< 0.33	0.33–0.50	0.5–1.0	~ 1	> 1
Effective shape of surfactant molecule	Cone	Truncated cone	Truncated cone	Cylinder	Inverted truncated cone
Preferred structure	Spherical micelles	Cylindrical micelles	Flexible bilayers, vesicles	Planar bilayers	Inverted micelles

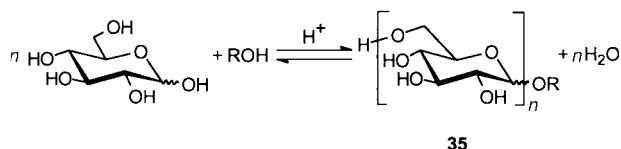


**Fig. 11** Aggregation behaviour of carbohydrate-derived amphiphiles as a function of the number of free hydroxy groups in the sugar and the length of the hydrophobic tail.

There has been for years great interest in biodegradable nonionic detergents prepared from carbohydrates as cheap and renewable feedstocks. Reviews, although somewhat dated, are available.<sup>29</sup> Examples of derivatives used commercially are shown in Scheme 16. Compound **32** is an (anhydro) sorbitol fatty ester, **33** a sucrose fatty ester, **34** a fatty acid glucamide and **35** an alkyl polyglucoside. These find application in the areas of detergents, cosmetics and foods.<sup>30</sup> Commercially the most important nonionic surfactants are the alkyl polyglycosides (APG's), prepared as illustrated in Scheme 17, and the total worldwide production of which is estimated to be 70,000–80,000 tons per year.



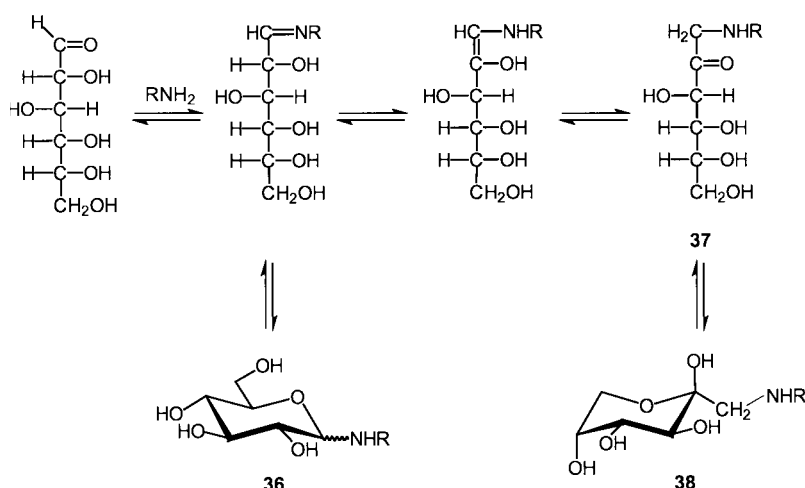
**Scheme 16**



**Scheme 17**

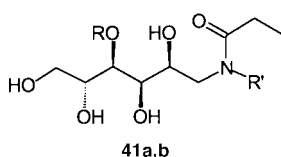
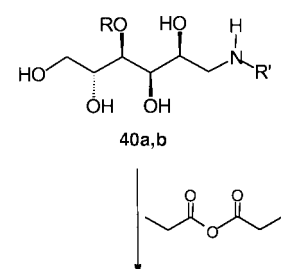
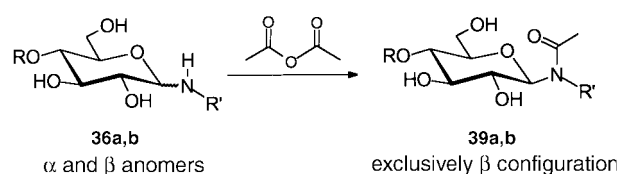
Let us first start with 'classical' structures of non-ionic detergents, namely condensation products of D-glucose or D-lactose with alkyl (*n*-octyl, *n*-decyl and *n*-dodecyl) amine. The reaction sequence for preparation, starting from D-glucose as an example, requires manipulation of the equilibrium illustrated in Scheme 18. If forcing conditions (low pH, high temperatures) are avoided *N*-alkyl- $\alpha,\beta$ -D-aldosyl amines **36** are isolated free of the Amadori rearrangement products **38** formed via tautomer **37**.<sup>31</sup>

Reduction with NaBH<sub>4</sub> or Pd/C under H<sub>2</sub> provides **40**. Both **36** and **40** are made more tractable by acylation with an anhydride. Acylation of **36** (Scheme 19) affords exclusively the  $\beta$ -anomer, which does not epimerize. As expected, these amides, including those of the linear compounds, are in general quite stable.

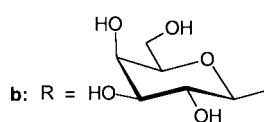


**Scheme 18**





**a:** R = H



R' = *n*-alkyl

**Scheme 19**

In Scheme 20 structures **39**, **41** are illustrated of stable surfactants that have been prepared. Compounds of type **41**

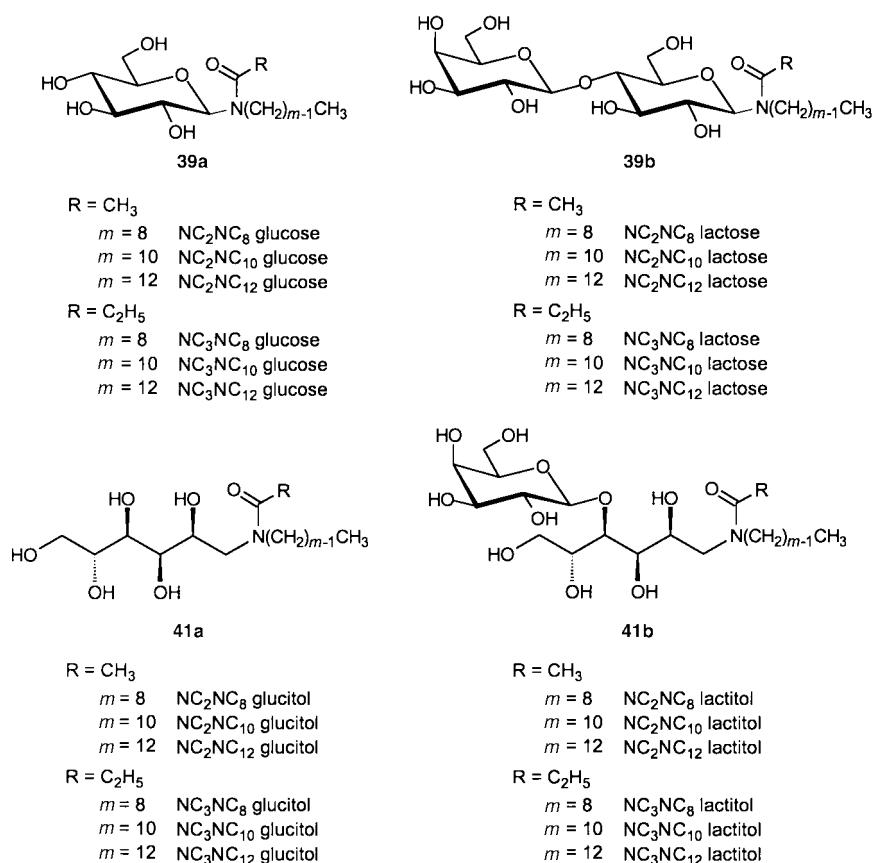
have been patented<sup>32</sup> and the potential for biomedical application of structurally related compounds has been pointed out.<sup>33</sup>

As anticipated virtually all of these compounds form micelles in water.<sup>34</sup> Brief consideration of some thermodynamic aspects of micellization is helpful to make clear the remarkably regular effects of structural change on aggregational behaviour. Compounds **39a,b** and **41a,b** will be considered. Since each 'compound' is a collection of structurally analogous derivatives with different chain lengths, it is convenient for tabulation (Fig. 12) to follow the nomenclature system shown in Scheme 20 whereby the sugar stem (**39a** = glucose, **39b** = lactose, **41a** = glucitol, **41b** = lactitol) is provided with a prefix NC<sub>*a*</sub>NC<sub>*b*</sub>, where *a* is the number of carbon atoms in the acyl group on nitrogen and *b* the number of methylene groups in the long polymethylene chain on the same nitrogen atom.

Critical micelle concentrations (cmcs) have the same order of magnitude (10<sup>-2</sup> to 10<sup>-4</sup> M) as generally shown by nonionic surfactants. The cmcs decrease regularly by roughly a factor of ten on increase of the length of the alkyl chain by two methylene groups (within the range studied) as nicely illustrated in the log<sub>10</sub> presentation shown in Fig. 12. A similar approximately tenfold decrease in cmc per two extra methylene groups is also shown by polyethoxylated surfactants and other nonionic surfactants.

The length of the alkyl chain is thus the major determining factor for the order of magnitude of the cmcs. From examination of Fig. 12 it can be seen that other factors such as the head group size (monosaccharide vs. disaccharide), shape (cyclic, acyclic, or combination thereof), length of the chain of the acyl group and the configuration of the hydroxy groups have a smaller influence on the cmc.

Glucose-derived surfactants have lower cmcs than the lactose-derived surfactants, owing to the smaller hydrophilic head group and, as a consequence, relatively larger hydrophobic unit. Surfactants with a reduced saccharide head group (glucitol, lactitol) have smaller cmcs than those with an intact cyclic



**Scheme 20**

### CMCs as a function of alkyl chain length for eight series of mono- and disaccharide derivatives

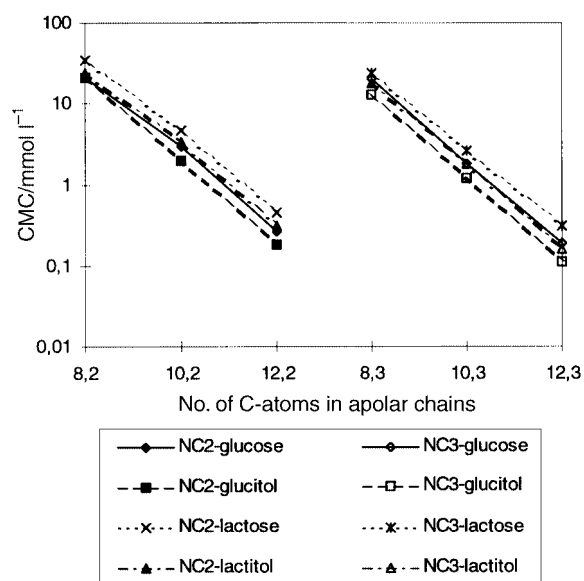


Fig. 12 Plot of  $\log_{10} \text{cmc}$  against chain length for compounds **39** and **41**. The coding for chain lengths is explained in the text.

structure. Probably the (hydrated) alditol head group is smaller, although data on volumes of appropriate hydrated carbohydrate-derived head groups are not available as far as we are aware.

Standard enthalpies of micellization ( $\Delta_{\text{mic}}H^\circ$ ), Gibbs energies of micellization ( $\Delta_{\text{mic}}G^\circ$ ), and entropies of micellization ( $\Delta_{\text{mic}}S^\circ$ ) are important in understanding micelle formation in aqueous solutions. Enthalpies of micellization can be accurately obtained using titration microcalorimetry. The standard Gibbs energy of micelle formation of a nonionic surfactant per mole of monomer is given by:

$$\Delta_{\text{mic}}G^\circ = RT \ln (\text{cmc} \cdot V_w^*)$$

Herein,  $V_w^*$  is the molar volume of water ( $0.018 \text{ dm}^3 \text{ mol}^{-1}$  at  $40^\circ \text{C}$ ) and the critical micelle concentration is given in  $\text{mol dm}^{-3}$ . The standard entropy of micelle formation per mole of monomer is:

$$\Delta_{\text{mic}}S^\circ = (\Delta_{\text{mic}}H^\circ - \Delta_{\text{mic}}G^\circ)/T$$

In general, the entropy term is the main driving force for micelle formation by nonionic surfactants. As micelles are formed, the hydrophobic hydration layers around the alkyl chains are broken down. This process is accompanied by a gain in entropy and represents the driving force for hydrophobic interaction within micelles. The causes of this hydrophobic effect have been discussed in detail.<sup>35</sup>

There are two contributions to  $\Delta_{\text{mic}}H^\circ$ : (i) an endothermic contribution from the head groups and (ii) an exothermic contribution from the alkyl chains. For alkylpolyglycol ethers the magnitude of the endothermic contribution of the head groups depends on the extent to which water is liberated into the bulk solvent upon micellization. As the degree of ethoxylation increases, the hydration and  $\Delta_{\text{mic}}H^\circ$  increase correspondingly. Data for  $\Delta_{\text{mic}}H^\circ$ ,  $\Delta_{\text{mic}}G^\circ$  and  $T\Delta_{\text{mic}}S^\circ$  are shown in Fig. 13. Again the structural changes lead to perfectly regular changes in the thermodynamic parameters for micellization. The disaccharide derivatives have more hydroxy groups and show an increase in  $\Delta_{\text{mic}}H^\circ$  (i.e. more endothermic) relative to their monosaccharide counterparts.

On going from  $\text{C}_8$  to  $\text{C}_{12}$  the exothermic contribution of the alkyl chain increases, whereas the endothermic contribution of the head group remains constant and, therefore, the enthalpy of micellization becomes more favorable. The contribution of each

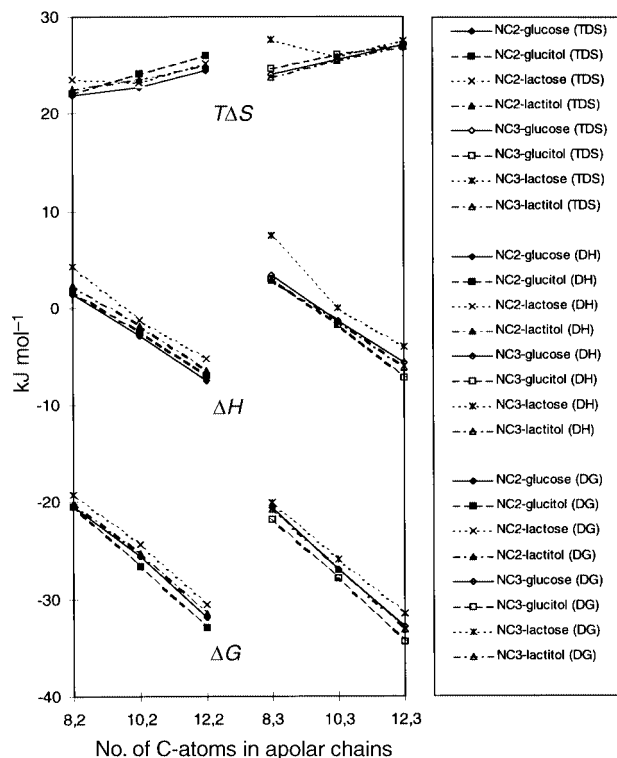


Fig. 13 Plot of thermodynamic parameters for micellization of four series of mono- and disaccharide derivatives **39** and **41**. The coding for chain lengths given on the ordinate is explained in the text.

methylene group on going from  $\text{C}_8$  to  $\text{C}_{12}$  to the enthalpy of micellization,  $\Delta_{\text{mic}}H^\circ$  ( $\text{CH}_2$ ), is approximately  $-2.4 \text{ kJ mol}^{-1}$ . This pattern is in good agreement with increments reported for other surfactants.

All estimates of  $\Delta_{\text{mic}}G^\circ$  are negative and become more so with increasing chain length. The contribution of each  $\text{CH}_2$  group to  $\Delta_{\text{mic}}G^\circ$  is on average  $-3.0 \text{ kJ mol}^{-1}$ . This is slightly lower than the Gibbs energy of transfer per  $\text{CH}_2$  of *n*-alkanes from water to pure liquid, because the environment of a given  $\text{CH}_2$  group in the interior of a micelle differs from that in the pure liquid.

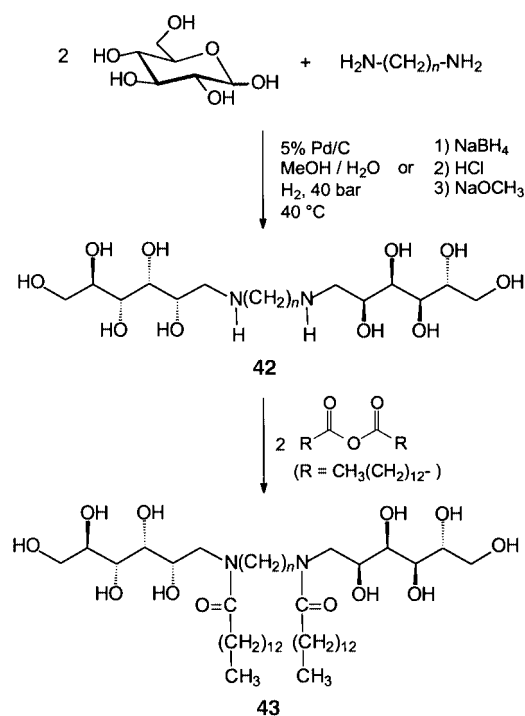
The entropy terms ( $T\Delta_{\text{mic}}S^\circ$ ) are positive and increase with increasing chain length. Values of  $T\Delta_{\text{mic}}S^\circ$  are large compared with those for ionic surfactants, for which the disrupting influence of ionic head groups on the ordering of water around the monomer is greater.  $T\Delta_{\text{mic}}S^\circ$  per  $\text{CH}_2$  averages roughly  $0.7 \text{ kJ mol}^{-1}$ . The main driving force of micellization at  $40^\circ \text{C}$  is the entropy term supported in some cases by an exothermic enthalpy term.

Let us examine the head groups. A lactose-derived head group is less favorable for micelle formation compared to a glucose-derived head group. The larger number of hydroxy groups increases the endothermic contribution to the enthalpy of micellization and renders the change in Gibbs energy less favorable. An alditol head group is more favorable for micelle formation than an aldose head group. This pattern is mainly caused by the changes in the enthalpy term and indicates that the hydration layers of the reduced carbohydrates are smaller. Consequently,  $\text{NC}_3\text{NC}_{12}$  glucitol exhibits the most favorable standard Gibbs energy of micellization.

Entirely in line with other carbohydrate-derived surfactants such as the alkyl polyglucosides and the aldonamides, and in agreement with the observed ease of micellization, the compounds described here also possess excellent detergency properties. We decided to go one step further and adapt the synthetic methodology, which had been worked out well, to prepare nonionic *gemini* surfactants. Gemini compounds with ionic head groups are known to have lower critical micelle concentrations (cmcs), to exhibit greater reduction of surface

tension, to have lower Krafft temperatures (the temperature at which the solubility of the surfactant equals the cmc, essentially the temperature at which the surfactant melts in water), better solubility properties and improved solubilization properties for hydrocarbons (oil).<sup>36</sup> At the inception of this work there was virtually nothing known about gemini surfactants with nonionic head groups; we realized that we would have to prepare a range of structures in order to delineate some of the basic elements of structure–aggregation behaviour for these types of compounds.

Again for reasons of practicality we have confined ourselves to D-glucose as starting material. The gemini compounds **42** are prepared as shown in Scheme 21, which is a slight adaptation of Scheme 19.



Scheme 21

The intermediate bolaamphiphiles **42** are obtained in a one-pot synthesis; if CH<sub>3</sub>OH:H<sub>2</sub>O ratios are chosen judiciously compounds **42** crystallize from solution after removal of Pd/C. Acylation with anhydrides to form **43** proceeds cleanly (attempts to increase the atom economy by using an acid chloride led to unsatisfactory results).<sup>37</sup>

The bolaamphiphiles **42** are in general too insoluble to be useful. The gemini compounds **43** obtained after acylation do not suffer from this problem. Krafft temperatures lie in the range of 30 to 40 °C, which is acceptable for applications. However, in the experiments 5 mol% sodium dodecanesulfonate was added to enhance solubility. Krafft temperatures lie in the range of 30 to 40 °C, which is acceptable for applications.

Examination of the lyotropic behaviour of **43**, both by optical microscopy and electron microscopy, revealed, in confirmation of expectations, a pronounced tendency to aggregate; in some cases quite dramatic myelins (worm-like channels) are obtained on contact with H<sub>2</sub>O. The structures of the myelins formed with 14-10-14 are shown in Fig. 14 (the first and last numbers of the shortened nomenclature for **43** give the length of the acyl group on nitrogen and the middle number gives the length of the connecting section between the two sugars).

Profound differences, dependent on structure, are observed. Compound 14-6-14 provides, as observed by electron microscopy, highly entangled thread-like micelles. This phenomenon influences physical properties: a solution of 14-6-14 (5 mM) is clear after preparation at 55 °C but turns blueish after 30 min at

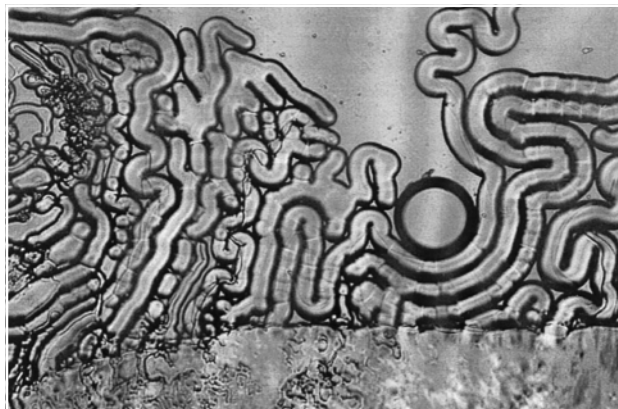


Fig. 14 Formation of lyotropic mesophases in a contact preparation of water and 14-10-14 at 45 °C; from top to bottom, water-myelin figures-L<sub>α</sub>-compound.

60 °C. At room temperature the solutions turn clear and become viscoelastic, a point established also by rheological studies. We ascribe this to the formation of thread-like micelles that become strongly entangled. A striking correspondence exists between aggregation behaviour and hydrocarbon solubilization (for example oil solubilization for tertiary oil recovery from shales and recovery of oil spills). In Table 3 a simplified summary is

**Table 3** Aggregates of bis(*N*-decanoyl-1-amino-1-deoxy-D-glucityl)alkanes and bis(*N*-alkanoyl-1-amino-1-deoxy-D-glucityl)decane observed by electron microscopy

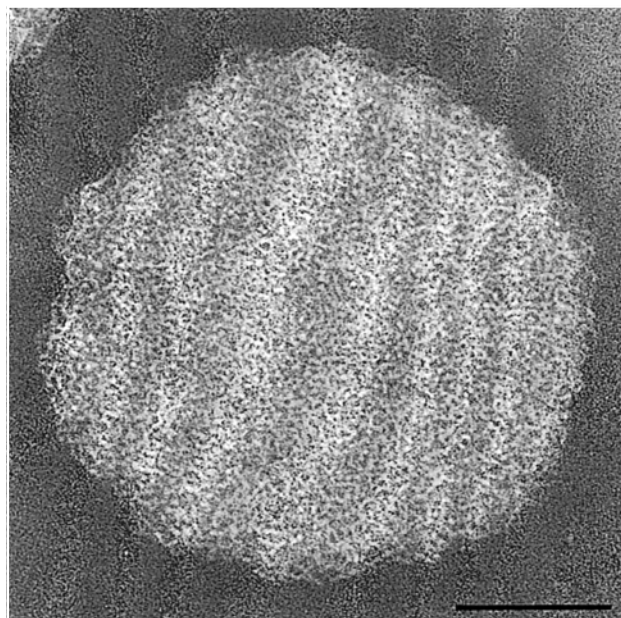
Compound	Appearance	EM
10-2-10	Clear	Thread-like micelles
10-4-10	Clear	Thread-like micelles, a few loops
10-6-10	Clear	<i>idem</i>
10-7-10	Blueish	<i>idem</i>
10-8-10	Milky	Thread-like micelles, loops and small clusters which grow in time
10-9-10	Milky	Clusters of thread-like micelles (60–500 nm; 2D wool balls)
10-10-10	Milky	Vesicles and tubular vesicles; no threads observed
10-12-10		Not soluble enough
5-10-5	Clear	Undefined material
6-10-6	Milky	Bilayered material
7-10-7	Blueish	<i>idem</i>
8-10-8	Clear	<i>idem</i>
9-10-9	Blueish	Vesicles (50–200 nm) and tubular vesicles
12-10-12	Blueish (55 °C)	Vesicles and sheets (35–250 nm)
14-10-14	Blueish (55 °C)	Vesicles
16-10-16	Blueish (55 °C)	Vesicles (a few ribbons)

given of chemical structure, visual appearance and the structures observed by electron microscopy. Compound 10-9-10 provides a dramatic example of the threading that can occur. In Fig. 15 the electron micrograph of negatively stained 10-9-10 is shown; the packing resembles a two dimensional wool ball. Compounds 10-6-10, 10-7-10 and 10-8-10 show similar behaviour although the electron micrographs are not as spectacular.

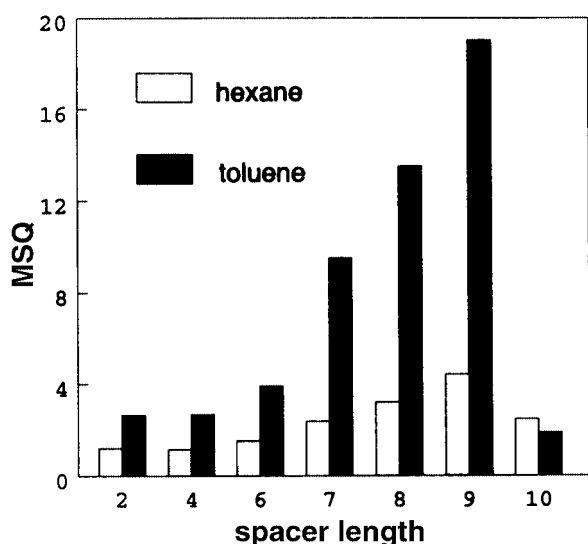
Compounds 9-10-9, 12-10-12, 14-10-14 and 16-10-16 form bilayers and vesicles (see Table 3). The capacity of some of these compounds to solubilize hexane and toluene is illustrated in Figs. 16 and 17. The solubilization capacity is high. Some reference compounds are shown in Fig. 18.

A detailed model of exactly how hydrocarbons fit into these ‘aggregates’ cannot be given at the present moment. However, the relationship between aggregation behaviour and capacity for the solubilization of hydrocarbons can hardly be coincidental. Future investigations will concentrate on questions such as the structure of the aggregates in the presence of hydrocarbon.





**Fig. 15** Negatively stained (2% PTA) electron micrograph of large clusters formed by 10-9-10. In this case, 7.5% NaLAS was added. However, the same clusters were observed when 5% NaLAS was added. The bar represents 100 nm.

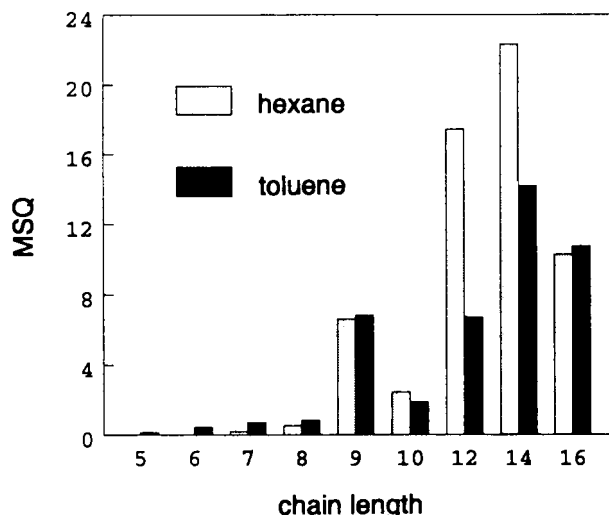


**Fig. 16** Solubilisation of hexane and toluene in aqueous solutions of carbohydrate-derived gemini surfactant series 10-s-10. The quantity MSQ is (moles solubilised oil in aqueous surfactant solution) – (moles oil in aqueous solution without surfactant)/(moles surfactant).

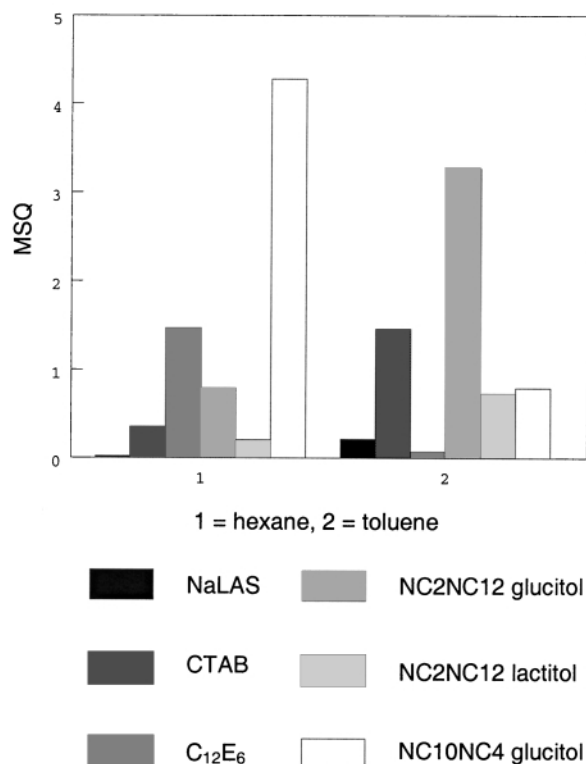
## 7 Conclusions

Sugars lend themselves to an astonishingly large range of structural variation, often by means of remarkably straightforward, high yield synthetic operations. The semi-synthetic derivatives developed here are of both academic and industrial interest. For example, the gemini surfactants described here will be the subject of a broad program designed to explore both the possibilities of commercial exploitation and the scientific implications.

This type of sugar chemistry is almost by definition multidisciplinary. Applications to semi-synthetic derivatives demand effective interfaces between synthetic chemistry and physically oriented areas of applications. Such applications require from all concerned a concentrated effort to learn each other's language. The molecular design that one brings to bear on the problem, if it is to have any chance of success, must be based on insight into the structural basis—at the molecular



**Fig. 17** Solubilisation of hexane and toluene in aqueous solutions of carbohydrate-derived surfactant series *m*-10-*m*.



**Fig. 18** Solubilisation of hexane and toluene in aqueous solutions of reference surfactants.

level—of aggregational behaviour. Such insight is now available and we hope that our own experiences with liquid crystals and surfactants may illustrate how to put that understanding into practice.

We feel that we have shown on a modest scale what some of the possibilities are, and, more importantly, where challenges and opportunities lie. Brief consideration of the multitude of functions of sugars, especially oligomers, in biochemistry—structural components, energy source, signaling functions in immune response, just to mention a few examples—indicates how great the possibilities are.

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